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Unifying Themes in Microbial Associations with Animal and Plant Hosts Described Using the Gene Ontology

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INTRODUCTION

Microbes have existed for more than 3.5 billion years and continue to evolve and adapt to an amazing diversity of environments that include extremes of temperature, salt, and acidity. Additionally, they form intimate relationships with other organisms, which may involve complex, highly specialized processes. Rapidly advancing DNA sequencing technology has opened an ever-widening window into the genomes of a broad diversity of microbes, including bacteria, apicomplexa, fungi, and oomycetes, as well as nematodes (24, 42, 55, 61, 70, 153, 214, 224). In concert, major advances in molecular genetics, biochemistry, and host genomics have delineated mechanisms underlying microbial symbioses, and many genes associated with these mechanisms have been characterized. The deluge of sequence information gains the most value once genes have been predicted from the sequences and functional descriptors have been attached to the predicted gene products. The process of adding functional descriptions to gene products is referred to as "functional annotation." Functional annotations arise directly from the characterization of genes and gene products reported in the literature and from transfers of annotations from characterized genes to uncharacterized ones based on sequence similarity. Comparisons among closely and distantly related microbes, based on sequence similarity, have

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greatly enhanced the value obtained from genome sequences by predicting common and diverging sets of functions among the microbes. However, when microbes are so divergent that sequence similarity is no longer readily identifiable or when common functions have been acquired via convergent evolution, gene products involved in similar functions can be missed. In such cases the functional descriptors may be compared, but for such comparisons to be useful, consistent terminologies are needed. In the past, descriptors for gene products have been inconsistent, as scientists may choose gene descriptors based on a concept of interest. For example, "effectors" are now generally accepted in the molecular host-microbe interaction scientific community to be defined as molecules that can alter the host cell structure or physiology or trigger defense responses, but they are still known in the nematode community as "parasitism genes" and in the human-microbe interaction community as "virulence factors."

The Gene Ontology (GO) consortium addressed the general issue of consistency in 1998 by adopting a standardized terminology to describe gene products from diverse taxonomic groups (12, 81). This work initially involved the mouse, *Drosophila melanogaster*, and yeast genomics communities, with bacteria being added in 2000. While work on the *Saccharomyces cerevisiae* yeast genome, and later on the genomes of prokaryotes, provided some terms for describing virulence factors, these were very limited. Thus, in 2004, the Plant-Associated Microbe Gene Ontology (PAMGO) interest group (http://pamgo.vbi.vt.edu/) was formed to work in collaboration with the GO consortium to develop GO terms (a word or phrase that represents the properties of a gene product defined under three main ontologies developed by the GO consortium) that describe gene products mediating processes involved in microbe-host interactions (63, 207, 213). Although the PAMGO consortium's focus was initially intended to be plant hosts, it quickly became evident that all but the most specific terms were also useful in the context of animal hosts as well. The PAMGO initiative has so far created over 900 terms (28, 122, 134, 208). Changes are constantly made to the GO database, and new terms are added as knowledge accrues.

In this review we identify some unifying themes common to diverse host-microbe associations and illustrate how the new GO terms facilitate a standardized description of the functions of gene products involved. We also highlight areas where new terms need to be developed, an ongoing process that should involve the whole community. For the purposes of this review, we will include "nematodes" when we mention "microbes" while acknowledging that some researchers prefer to make a distinction between them.

GENE ONTOLOGY

The Gene Ontology is a collaborative effort that began in 1998 with scientists working on the genomes of three model organisms, *Drosophila* (FlyBase), *Saccharomyces* (*Saccharomyces* Genome Database), and mouse (Mouse Genome Informatics) (12) (http://www.geneontology.org/). The main aim of the GO consortium is to create universal descriptors, which can be used to describe functionally similar gene products and their attributes across all organisms. This had become necessary because different life science communities often use different terminologies to describe similar concepts. Thus, searching the literature to find information on a specific subject area has been an arduous task for the biologist. The GO includes three controlled, structured vocabularies stored as ontologies that describe gene products on the basis of their molecular function(s) (the Molecular Function ontology), the biological process(es) in which they are involved (the Biological Process ontology), and the location(s) in the cell where they act (the Cellular Component ontology). Each ontology is made up of terms that relate to each other in a parent-child fashion, forming frameworks called directed acyclic graphs (DAGs). A DAG bears similarity to hierarchical structures. However, within a DAG, a child term can have multiple parents (Fig. 1). The GO also requires that the parent-child relationship be categorized into one of three possibilities: "is_a", "part_of", or "regulates" (http://www.geneontology.org/GO.ontology.structure.shtml). Associated with each GO term is a numerical identifier, a term name, a comprehensive definition, a set of synonyms used interchangeably with this particular name in the literature, and comments guiding the use of the term (Fig. 2). In parallel with the process of developing standardized terms is the ongoing work of associating appropriate terms with products of genes in organisms of interest, a process known as annotation. The GO annotation process, illustrated in the following paragraph, includes a detailed system for recording the evidence used in the annotation. The core of the evidence record consists of evidence codes and associated references. Evidence codes describe the type of information used for an annotation. Examples include "inferred from mutant phenotype" (IMP) or "inferred from sequence or structural similarity" (ISS). The references describe the source where information was obtained or the method used for making an annotation. Examples include PUBMED identifiers (PMID) for literature references and the GO standard reference collection (http://www.geneontology.org/cgi-bin/xrefs.cgi). More on the annotation process and evidence documentation can be found at http://www.geneontology.org/GO.annotation.shtml and http://www.geneontology.org/GO.evidence.shtml, respectively. Ideally, the development and official acceptance of new GO terms are processes that require participation from as many experts in the scientific community as possible. Some terms are speedily incorporated into the official GO, while others undergo lengthy discussion before acceptance.

Examining some current GO terms associated with the *Pseudomonas syringae* pv. *tomato* DC3000 effector HopN1 illustrates the GO annotation process. Searching from the GO home page (http://www.geneontology.org) for the gene "HopN1" via the GO search engine AmiGO reveals the eight current term associations (i.e., annotations) as well as the evidence and reference for each. Among these are two GO terms from the Molecular Function ontology, "GO:0008234 cysteine-type peptidase activity" and "GO:0051087 chaperone binding." For each term, the reference listed is PMID:15469508, a paper by López-Solanilla and coworkers (124). Detailed in this paper is evidence supporting these annotations, including an *in vitro* assay testing purified HopN1 and mutant versions of it for cysteine protease activity using resorufin-labeled casein as a substrate. Also described are experiments using two plasmid constructs, one expressing a HopN1-Cya fusion and the other being the then-putative chaperone specific for this effector. Tests done with bacteria inoculated into tomato

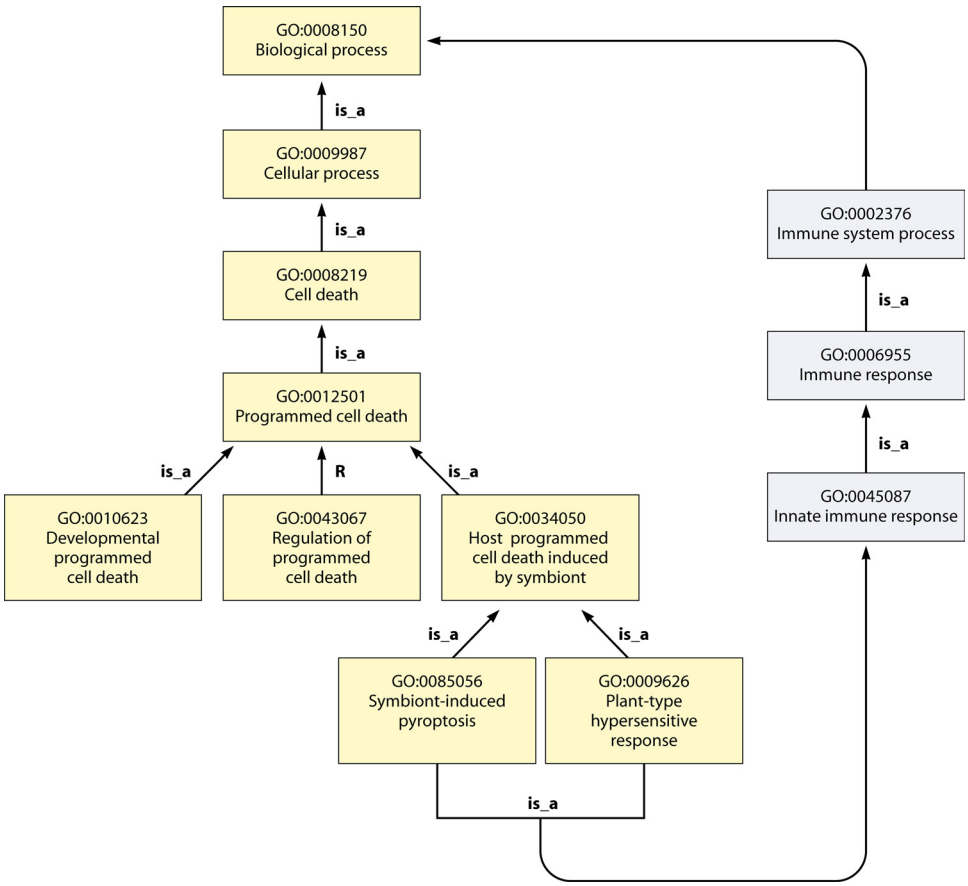

FIG. 1. Simplified directed acyclic graph (DAG) illustrating several terms describing different types of programmed cell death (PCD). Note that the last two terms have two parents, indicating two pathways via a series of more-general terms (shown in sandy brown and gray) to the root of the Biological Process ontology. "is_a" and "regulates" (R) are two of the three relationships that exist between parent and child terms within the DAG. (For more on term relationships, see http://www.geneontology.org/GO.ontology.structure.shtml.)

leaves indicated that HopN1 is translocated into plant cells and at a significantly higher level in the presence of the chaperone. The *in vitro* assay is a good example of the GO evidence code "inferred from direct assay" (IDA), and searching the GO terms using AmiGO for "cysteine protease" leads to the GO term GO:0008234 (named above), where "cysteine protease" is listed as an exact synonym. The evidence for "GO:0051087 chaperone binding" is less direct and is described by the evidence code "inferred from genetic interaction" (IGI). IGI allows the naming of the interacting partner, in this case the chaperone to which HopN1 binds. This is indicated by information placed into a special field of the GO annotation file known as the "with" column; in this case, the UniProtKB accession number for the type III chaperone protein ShcN to which HopN1 binds would be included. Finding the correct GO term is relatively straightforward, involving a search via AmiGO for the term "chaperone" and then selection from the list of GO terms provided.

The Plant-Associated Microbe Gene Ontology Initiative

Since the inception of the GO consortium in 1998, several additional groups working on plant, animal, and microbial genomes have joined the consortium. The Plant-Associated Microbe Gene Ontology (PAMGO) interest group joined the GO consortium in 2004 to extend the GO to include terms describing processes involved in microbial-host interactions (63, 207, 213). The PAMGO initiative is a collaborative effort spanning several academic institutions: the Virginia Bioinformatics Institute at Virginia Tech, Cornell University, Wells College, the University of Wisconsin at Madison, North Carolina State University, the J. Craig Venter Institute (The Institute for Genomic Research [TIGR] at the outset of the project), and, more recently, the University of Maryland School of Medicine. It includes scientists working on the genomes of bacteria, oomycetes, fungi, and nematodes. An initial term development effort in 2004 produced a set of higher-level biological process terms that could be used to describe general processes often encountered by microbes interacting with their hosts. The PAMGO collaborators built these higher-order terms to be appropriate for describing gene products of all types of symbionts (e.g., parasites, commensalists, and mutualists), including prokaryotes and eukaryotes that associate with plant or animal hosts. A key step in the term development process was the creation of the GO symbiosis term and its proper definition and placement. The PAMGO group defined symbiosis as a broad continuum ranging from mutualism through commensalism to parasitism, in keeping with its original definition by de Bary (43). This continuum is embodied in the wording

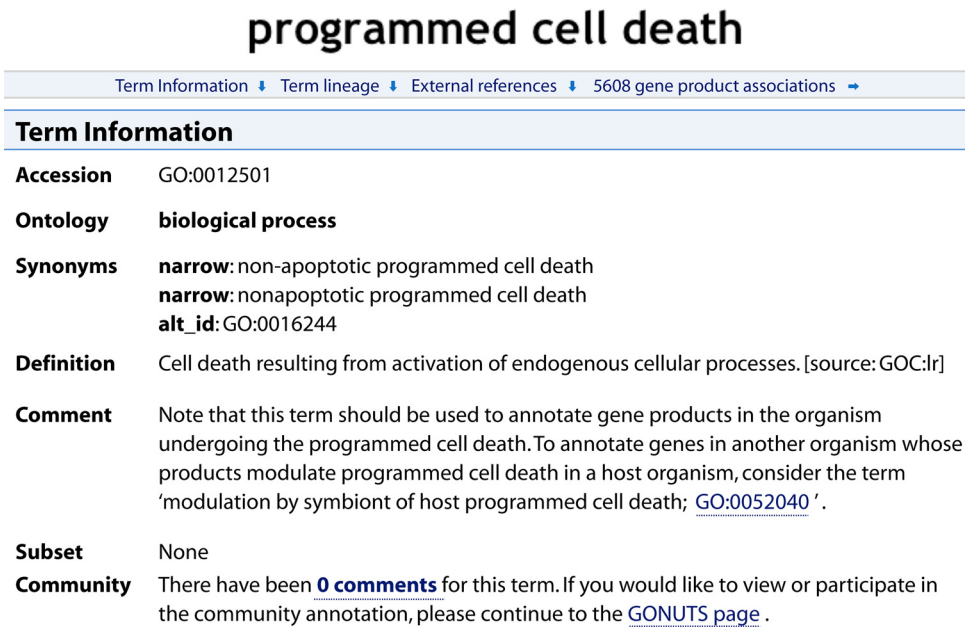

FIG. 2. Gene Ontology term information page. Shown is an example of a "term information page" as seen via the official Gene Ontology browser AmiGO (http://amigo.geneontology.org). Featured on this page are the required information associated with the term "GO:0012501 programmed cell death" and also the number of genes (5,608) currently annotated to this term. Note the synonyms for the primary term and also a comment directing GO curators to the proper usage of the term. Keyword searches using words from the primary term or synonyms will yield this page.

"GO:0044403 symbiosis, encompassing mutualism through parasitism." The PAMGO consortium strongly discourages the usage of "symbiosis" as a synonym for "mutualism." The term is a child of "GO:0044419 interspecies interaction between organisms" and can encompass intimate interactions between any sets of organisms, whether or not one is a microbe. However, to accommodate interactions between a host and a microbe, the definition of the term includes the statement that "the term host is usually used for the larger (macro) of the two members of a symbiosis and the smaller (micro) member is called the symbiont organism." In accordance with that view, this review will refer to microbes that interact with hosts in any manner along the symbiotic continuum as symbionts. Child terms of the symbiosis node include general terms such as "GO:0051824 recognition of other organism during symbiotic interaction," "GO:0052192 movement in environment of other organism during symbiotic interaction," and "GO:0051825 adhesion to other organism during symbiotic interaction" (Fig. 3A). As the annotation of gene products from selected genomes proceeded on the basis of experimentally supported functional data in the scientific literature, the need arose for more specific terms to describe more detailed functional characterizations. The following is an example of the more detailed terms that can be incorporated under a more general parent term. Under the term "GO:0044409 entry into host," there are several more-specific terms, including "GO:0030260 entry into host cell," "GO:0044411 entry into host through host barriers," "GO:0044410 entry into host through natural portals," and "GO:0075052 entry into host via a specialized structure." Under the term "GO:0075052 entry into host via a specialized structure," there are even-more-granular (specific) terms that describe specialized structures used by filamentous symbionts to facilitate host entry. The value of this framework is that all gene products described with the more-granular terms are automatically described by the parent terms as well. All the GO terms designated for processes involved in host-microbial interplay (irrespective of whether the association is mutualistic, commensalistic, or parasitic or whether the hosts are plants or animals) are placed under "GO:0044403 symbiosis, encompassing mutualism through parasitism," which connects to the root "GO:0008150 biological_process" through intermediate terms like "GO:0044419 interspecies interaction between organisms" and "GO:0051704 multiorganism process."

The Cellular Component ontology contains terms used to describe the locations of gene products within cells, tissues, structures, or molecular machines. Since a number of the terms introduced by the PAMGO consortium describe the action of microbial gene products on host cells, it was necessary to introduce new terms to depict the activities of microbial gene products that act within the host cell as opposed to the microbial cell. The introduction of "GO:0043657 host cell" and its child terms serves this purpose (Fig. 3B). Terms were also introduced to describe host structures that are formed specifically during interactions with a microbe, such as "GO:0043664 host peribacteroid membrane" and "GO:0020005 symbiont-containing vacuole membrane." Currently, the PAMGO consortium has contributed over 900 terms to the GO database. As part of the normal annotation process, the GO requires a taxon identification (ID) for the organism whose gene products are being annotated. To accommodate multiorganism processes, the GO consortium introduced a second taxon identifier to ensure that the taxon identifiers of both interactors—the microbe and the host—could be recorded for those situations where a gene product produced by the microbe carries out its function in a different organism, the host. For more on annotation guidelines, see http://www.geneontology.org/GO.format

FIG. 3. Tree views of two key PAMGO terms as seen via the official Gene Ontology browser AmiGO (http://amigo.geneontology.org). I, P, and R denote the three relationships, "is_a", "part_of", and "regulates", that exist between parent and child terms within the DAG. (For more on term relationships, see http://www.geneontology.org/GO.ontology.structure.shtml.). (A) Tree view of "GO:0044403 symbiosis encompassing mutualism through parasitism" and its child terms. (B) Tree view of "GO:0043657 host cell" and some of its child terms. In the last three terms in this tree, "symbiont-containing vacuole" is the GO synonym for parasitophorous vacuole.

.annotation.shtml. The sections below will highlight the use of the GO to conceptualize shared and divergent mechanisms involved in the interplay of diverse symbionts with their plant or animal hosts.

ADHESION STRATEGIES

Adhesion is a crucial step for maintaining the location of symbionts within or on their hosts as well as being central to initiating new colonizations or infections. Adhesion is often facilitated by adhesins, which are molecules on the surface of microorganisms that mediate adherence to host cell surfaces, receptors, membranes, or the extracellular matrix (ECM). Many symbionts, including bacteria, oomycetes, and fungi, produce monomeric adhesins that facilitate host attachment (106, 109, 162, 175). These molecules are sometimes recognized by hosts as microbe-associated molecular patterns (MAMPs) (110, 212) and thus risk triggering the host surveillance machinery (more details on MAMPs ap-

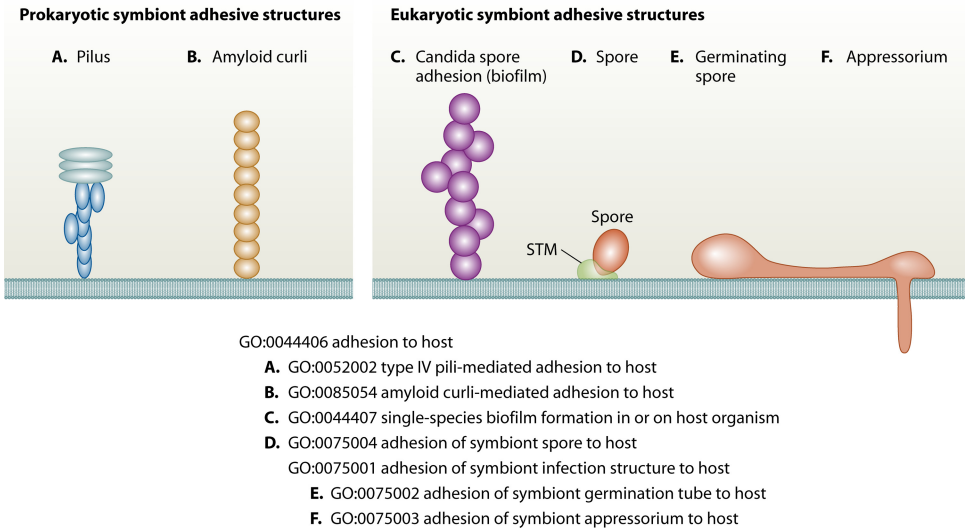

FIG. 4. Schematic representation of adhesion mechanisms of prokaryotic and eukaryotic symbionts on plant and animal hosts described with relevant GO terms. On the left are prokaryotic adhesive structures: pilus (A) and amyloid curli (B). On the right are eukaryotic adhesive structures: *Candida* biofilm attaching to the host cell (C), spore anchored to the host by the spore tip mucilage (STM) (D), germinating spore (E), and appressorium (F). Corresponding GO terms are labeled with the same letter as the adhesive structure. All specific terms fall under the parent term "GO:0044406 adhesion to host."

pear below). Symbiotic bacteria may also possess macromolecular assemblies such as pili to facilitate attachment to the host (14, 94, 110). Adhesins also facilitate the tenacious anchorage of specialized infection structures of phytopathogenic fungal and oomycete symbionts to their hosts prior to infection (75, 211). The GO has explicit terms to describe adhesion mechanisms, which are located under the umbrella term "GO:0022610 biological adhesion" in the Biological Process ontology. The child term pertaining to microbial adhesion mechanisms in symbiont-host associations is "GO:0044406 adhesion to host." Depending on the extent of the characterization of these adhesive gene products, more-specific terms may be needed. We illustrate how the GO unites adhesion strategies in diverse symbionts with plant or animal hosts by using examples of adhesive molecules or structures from bacteria, apicomplexans, oomycetes, and fungi (Fig. 4).

Adhesion Strategies of Bacterial Symbionts

Bacterial symbionts include medically important pathogens (e.g., *Escherichia coli*, *Salmonella*, *Shigella*, *Yersinia*, *Streptococcus*, and *Staphylococcus*) and agriculturally important pathogens (e.g., *Pseudomonas*, *Xanthomonas*, *Ralstonia*, *Erwinia*, and *Agrobacterium* species). Many of these symbionts have been shown to produce monomeric proteinaceous adhesins (afimbria adhesins), including those that bind to components of the extracellular matrix (ECM) of the host. *Streptococcus* and *Staphylococcus* species produce cell wall-anchored proteins called MSCRAMMs (microbial surface components recognizing adhesive matrix molecules), which bind to the host ECM and are implicated in infection (189–191). Specifically, *Streptococcus pyogenes* (responsible for cutaneomucosal infections) produces the adhesin SfbI (also called protein F1) that binds fibronectin (a glycoprotein found in the ECM and body fluids of vertebrates), thus triggering host intracellular signaling and leading to defense responses (54, 137, 138). Attachment to host cells is also important in enabling the secretion of effector proteins through bacterial secretion systems. For example, in the enteropathogenic *Yersinia* species, three adhesins, invasin, YadA, and Ail, have been shown to promote the type III secretion system (T3SS)-dependent delivery of *Yersinia* effector proteins (179). In parallel with pathogens, the adhesion of commensal lactobacteria to the mucus layer of the gut is mediated by proteins that include the extracellular mucus-binding protein (Mub) (178) and the lectin-like mannose-specific adhesin (Msa) (168). Extensive characterization of bacterial attachment to host tissues by various adhesins and the role of these molecules in pathogenesis have been reported for many animal pathogens (for a review, see reference 110); however, studies of plant systems are very limited. Members of one set of gene products that bear a resemblance to the family of hemagglutinin-like proteins originally identified in animal bacterial pathogens (*Bordetella* and *Yersinia* spp.) have also been identified in many necrogenic bacterial pathogens of plants (including *Ralstonia*, *Xylella*, *Pseudomonas*, and *Erwinia* spp.) (176).

In addition to monomeric adhesin proteins exposed on the outer surface of their cells, most bacteria express additional adhesins on macromolecular assemblies that extend from the bacterial cell to the host, allowing for host interactions at a distance. Adhesive macromolecular assemblies include the well-characterized pilus structures (type I pili, P pili, type IV pili, and the T pilus) found in Gram-negative bacteria associated with plant and animal hosts. The role of the T pilus in adhesion in the plant crown gall pathogen *Agrobacterium tumefaciens* is still under investigation; however, recent studies suggest that VirB5, which is a minor component of the pilus, may play an adhesive role (8, 9, 14). Sticky amyloid curli found in most enteric pathogens and commensals of animals (e.g., *E.*

coli and *Salmonella* spp.) (15, 152) are also involved in adhesion to the host. However, unlike the pili, amyloid curli are not known to exhibit any clear ligand-binding specificity (110).

As mentioned above, GO terms describing proteinaceous adhesins in all symbionts fall under the umbrella term "GO:0044406 adhesion to host." The gene products forming the macromolecular assemblies can potentially be described further with more-specific terms such as "GO:0052001 type IV pilus-dependent localized adherence to host" and "GO:0085054 amyloid curli-mediated adhesion to host."

Adhesion Strategies of Eukaryotic Symbionts

Fungal and oomycete symbionts, like their bacterial counterparts, also produce adhesive molecules or structures for host attachment as a first step in interacting with their plant or animal host. Fungal symbionts share some morphological features with their oomycete counterparts, a result of convergent evolution as they belong to different kingdoms. Like bacterial symbionts, symbiotic fungi and oomycetes produce monomeric proteinaceous adhesins that facilitate attachment to their plant or animal hosts. The GO collects all these adhesive proteins and their bacterial counterparts under the umbrella term "GO:0044406 adhesion to host."

Adhesins have been extensively characterized for the fungus *Candida albicans*, a normally commensal symbiont of humans that can cause mucosal infections in healthy individuals and which may be fatal in immunocompromised individuals (165, 186). Several components of the *Candida* cell wall, such as chitin, β-glucan, and lipids, may be involved in the adhesion process, although specific attachment proteins (adhesins) have been identified and have been described as being the most significant mediators in the interaction (56). These include members of the family of agglutinin-like sequences (Als). Specific members of the Als family of adhesins, such as Alslp and Als5p, are also potentially important for the coadhesion of single or mixed microbial communities (bacteria or fungus) in biofilms (111). *C. albicans* cells interact with a wide variety of host extracellular matrix molecules (collagen, fibronectin, and laminin) that promote adhesion to host surfaces (156; reviewed in references 103 and 194).

Following dissemination, many fungal and oomycete spores attach to plant hosts, aided by adhesins prior to the penetration of the host by emerging germ tubes or via appressoria that differentiate from the germ tubes. In the case of the rice blast fungus, *Magnaporthe oryzae*, the extrusion of the spore tip mucilage (STM) under moist conditions serves to anchor the conidial spore to the hydrophobic rice leaf surface (74). The composition of the *M. oryzae* mucilage includes α-linked mannosyl and glucosyl residues as well as lipids and proteins. Proteinaceous components of the STM facilitating the attachment of the spore to the host can potentially be described with the GO term "GO:0075004 adhesion of symbiont spore to host." An oomycete example of a gene product annotated with "GO:0075004 adhesion of symbiont spore to host" is the product of the *Phytophthora cinnamomi* spore-adhesive gene *PcVsv1* (79, 175). The PcVsv1 protein has 47 copies of the thrombospondin type 1 repeat, a motif found in adhesins of human-pathogenic protozoans, notably in the malaria pathogen *Plasmodium falciparum*. The *P. falciparum* thrombospondin-related adhesive protein (TRAP)-like protein (TLP) has been suggested to play a role in the traversal of hepatocytes by sporozoites, potentially anchoring the sporozoite to the hepatocyte prior to, and during, movement into the cell (139). Other adhesins of the malarial parasite include the well-characterized *P. falciparum* erythrocyte membrane protein 1 (PfEMP-1). Expressed on the surface of erythrocytes, PfEMP-1 acts as a cell adhesion molecule to sequester infected erythrocytes within the microvasculature by binding to the surface of endothelial cells, thus preventing clearance by the spleen (199). PfEMP-1 is best described with "GO:0020035 cytoadherence to microvasculature, mediated by symbiont protein," a sibling term (sharing a common parent) of "GO:0075004 adhesion of symbiont spore to host."

The coadhesion of symbiont cells within biofilms can potentially be described with "GO:0044407 single-species biofilm formation in or on host organism," where only one species of symbiont is involved, or "GO:0044401 multispecies biofilm formation in or on host organism," where different species of symbiont are involved. An example of the latter is where both *Candida* and bacteria form the components of a biofilm (i.e., plaque) in the oral cavity. In cases where the adhesion process results in pathogenesis, the associated gene product can be annotated with the term "GO:0009405 pathogenesis" as well.

EFFECTOR DELIVERY SYSTEMS

The essential role of extracellular proteins in symbiont-host interactions has made them a subject of intense study. Among these proteins are host cell-targeted effectors, which are translocated via various delivery systems by bacteria, protozoa, oomycetes, fungi, and nematodes into their eukaryotic hosts (plants or animals). These delivery systems and their substrates (effectors) alter host physiology while promoting the survival and growth of the symbiont in the host environment. Delivery systems and their substrates (effectors) can be united under specific GO terms in the Cellular Component and Biological Process ontologies, respectively. Interactions with hosts mediated by effectors can be described by Biological Process terms under "GO:0052048 interaction with host via secreted substance during symbiotic interaction." Using appropriate GO descriptions, in the following sections we highlight common themes underlying effector delivery in both prokaryotic and eukaryotic symbionts in plant and animal hosts.

Prokaryotic Effector Delivery Systems

Bacteria have evolved diverse secretion machineries that translocate substrates across the cell envelope into the extracellular milieu or the host. The delivery systems in bacteria are numerically distinguished as types I through VI (91, 210) plus a recently identified type VII system in Gram-positive bacteria (1). Substrates translocated via these secretory systems include nucleic acids, proteins, and nucleoproteins. Among these secretion systems, the type II secretion system (T2SS), type III secretion system (T3SS), and type IV secretion system (T4SS) deliver many proteins (effectors) central to pathogenicity and virulence (reviewed in references 33, 38, 40, and 210). In addition, the T4SS mediates the translocation of single-stranded DNA (ssDNA) (T-DNA) into the host cell (reviewed in refer-

ence 7). Effector delivery via the T2SS requires two or, in some cases, three steps. There are separate mechanisms for proteins to pass the bacterial inner membrane (IM) and the bacterial outer membrane (OM) and a third mechanism for those type II effector (T2E) proteins that cross the host plasma membrane. On the other hand, effector delivery via the T3SS and T4SS is a one-step process out of the bacterial cytoplasm and directly across the host plasma membrane into the host cell, or sometimes into the extracellular milieu ("GO:0043655 extracellular space of host"), for type IV effectors (T4Es).

Type II secretion. The T2SS apparatus, described with the GO term "GO:0015627 type II protein secretion system complex," is made up of at least 12 gene products that form a multiprotein complex. Prevalent among the Gram-negative proteobacteria, it is required for the virulence of the human pathogens *Vibrio cholerae*, *Legionella pneumophila*, and enterotoxigenic *E. coli* and of the plant pathogens *Ralstonia solanacearum*, *Pectobacterium atrosepticum* (*Erwinia carotovora* subsp. *atroseptica*), *Dickeya dadantii* (*Erwinia chrysanthemi*), and *Xanthomonas campestris* pv. *campestris* (33, 57, 185). The T2SS complex spans the periplasmic space and is specifically required for the translocation of secreted proteins (from the universal Sec and twin-arginine [Tat] pathways) across the outer membrane (57, 181, 219) (Fig. 5A). When the bacterium is associated with a host, these secreted proteins, which include toxins, cell wall-degrading enzymes, and hydrolytic enzymes, are released into the extracellular milieu of the host. Some toxins secreted via the T2SS can subsequently enter host cells by receptor-mediated endocytosis (184). Secreted proteins traveling through diverse secretion systems to the host can be annotated with child terms of "GO:0052048 interaction with host via secreted substance during symbiotic interaction" according to the name of the specific secretion system employed. Accordingly, T2SS substrates can be annotated with "GO:0052051 interaction with host via protein secreted by type II secretion system." Furthermore, the gene products facilitating the secretion process, but not those actually secreted into the host cell, would be best described with the Biological Process term "GO:0015628 protein secretion by the type II secretion system"(210).

Type III secretion. The T3SS has been identified in many Gram-negative animal- and plant-associated bacteria, and effectors delivered via the T3SS are responsible for the virulence of several pathogens of plants and animals. The T3SS consists of a series of subcomplexes that together provide a continuous path across the bacterial IM and OM in addition to, in many cases, the plasma membrane of the host (Fig. 5A). From the OM, the T3SS consists of a hollow needle-like structure in animal pathogens or a pilus in plant pathogens, which terminates in a translocation structure (translocon) that inserts into the plasma membrane of the host (59, 112, 127, 142). The pilus of plant pathogens, unlike the needle of *Yersinia* and other animal pathogens, does not have a fixed length, presumably because of the need to cross the extra barrier of the cell wall of the host plant cell. The structure and function of the T3SS apparatus have been extensively studied for animal pathogens in the genera *Yersinia* and *Salmonella* and plant pathogens in the genera *Pseudomonas*, *Xanthomonas*, and *Ralstonia.* Conserved proteins in the basal structure of the T3SS of plant-associated bacteria are named in reference to their *Yersinia* secretion (Ysc) homologs. For example, the YscC homolog in pathogens is designated HrcC (hypersensitive response and conserved), and in the mutualistic organism *Rhizobium*, it is designated RhcC (*Rhizobium* conserved). These conserved gene products, together with others composing the secretion apparatus, can be annotated with a Cellular Component term, "GO:0030257 type III protein secretion system complex." Unlike the T2SS, which transports secreted proteins to the host extracellular milieu, the T3SS usually mediates virulence by injecting bacterial proteins (effectors) directly into eukaryotic host cells (20, 67, 78, 151, 193). The ability of the T3SS to deliver effector proteins directly into the host cytosol was first demonstrated in the case of the *Yersinia* effector proteins called Yops (*Yersinia* outer proteins) (180). Subsequently, several groups demonstrated that type III effectors of phytopathogenic bacteria in the genera *Pseudomonas* and *Xanthomonas* function inside plant cells, indicating that their T3SSs, like the *Yersinia* T3SS, are also involved in the delivery of effector proteins directly into the host cytosol (68, 120, 203, 215). Many plant pathogen effectors have designations like Hop (Hrp outer protein) or Xop (*Xanthomonas* outer protein), but others are known as Avr (avirulence) proteins, and there is no unified system for all plant pathogens. *Rhizobium* spp., which are nitrogen-fixing bacteria that engage in mutualistic associations with leguminous plants, also possess a T3SS and inject Nops (nodulation outer proteins) into host cells (217). The gene products involved in the T3SS secretion process can be described with the Biological Process term "GO:0030254 protein secretion by the type III secretion system." The effector proteins that mediate interactions with the host are, in contrast, annotated with the term "GO:0052049 interaction with host via protein secreted by type III secretion system" and, where appropriate, its child term, "GO:0052057 modification by symbiont of host morphology or physiology via protein secreted by type III secretion system."

Type IV secretion. T4SSs are found in both Gram-negative and Gram-positive bacteria. Compared to other secretion systems, they are quite versatile. In Gram-negative bacteria, they mediate the secretion of monomeric proteins, toxins, nucleic acids, and nucleoprotein complexes across cell membranes and into the extracellular milieu or the cytoplasm of their host (reviewed in references 7, 62, 123, and 131). In *Agrobacterium*, T4SSs are formed by at least 12 proteins, termed VirB1 to VirB11 and VirD4, while other T4SS-containing pathogens may have subsets of these structural components (reviewed in reference 166). The gene products constituting the structural component of the T4SS can potentially be assigned the GO term "GO:0043684 type IV secretion system complex." Among these components are the three ATPases VirD4, VirB4, and VirB11, which power the secretion machinery. T4SSs are found in bacteria pathogenic to plants, animals, and humans. For example, in *Helicobacter pylori*, the T4SS delivers the CagA protein into gastric epithelial cells, and this is instrumental in the development of gastric carcinoma (82). In *Agrobacterium*, besides virulence effectors, the T4SS delivers an ssDNA into the plant host (as mentioned above). The GO collects both animal- and plant-pathogenic effectors delivered via the T4SS under the GO term "GO:0052050 interaction with

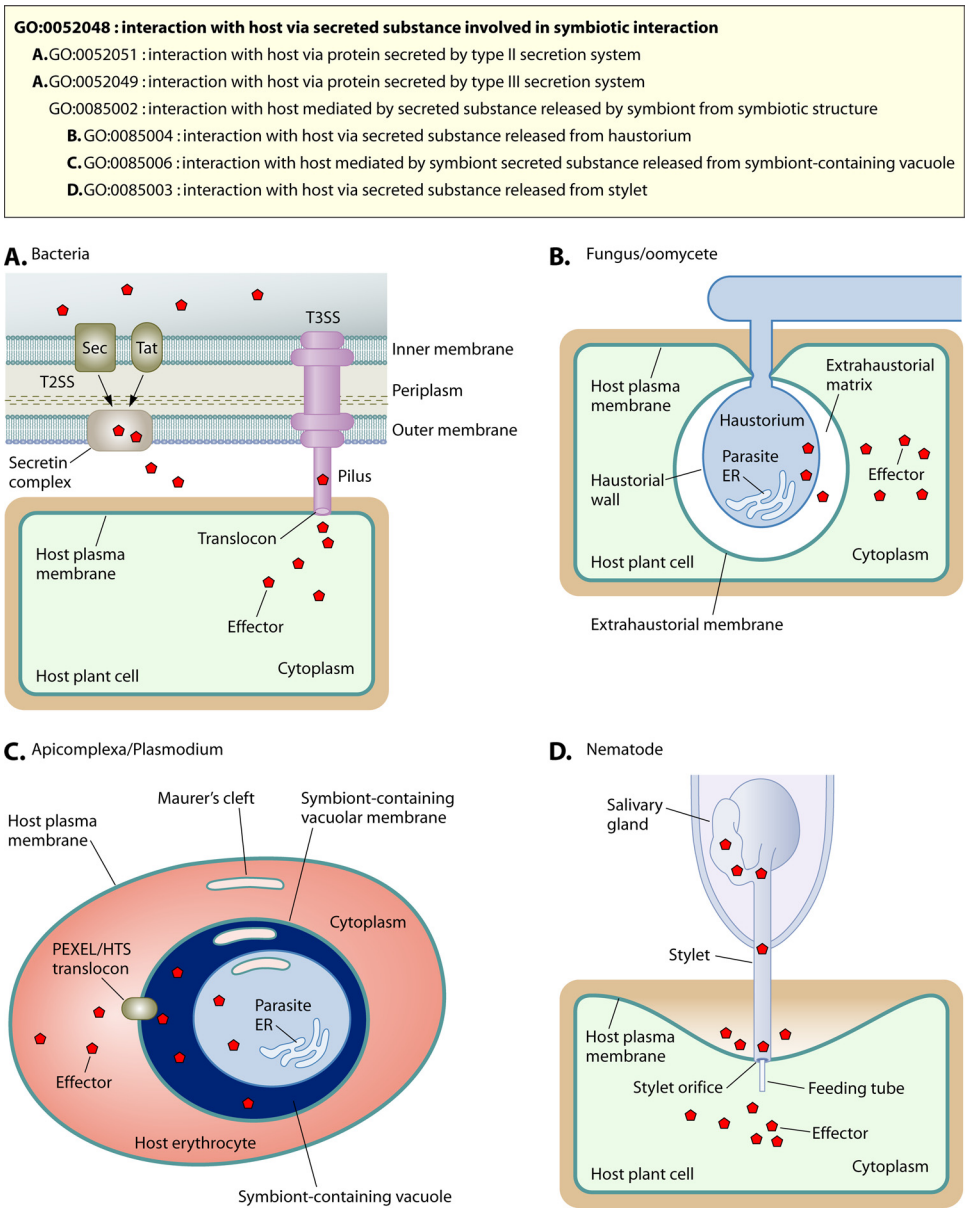

FIG. 5. Schematic representation of selected structures from diverse symbionts employed in effector delivery in both plant and animal hosts. (A) Bacterial T2SS and T3SS. The effectors are exported via the Sec or Tat system and subsequently translocated to the extracellular milieu via the T2SS. The T3SS translocates effector proteins across the host plasma membrane into the host cell via the translocon. (B) The haustoria of filamentous symbionts such as fungi and oomycetes are formed when a hypha pierces the cell wall and invaginates the cell membrane. Effectors are secreted into the extrahaustorial matrix, where some may cross the extrahaustorial membrane into the host cytoplasm. (C) Parasitophorous vacuole of *Plasmodium*. During invasion of the erythrocyte, the parasite remains enveloped in the host plasma membrane, which becomes the parasitophorous vacuolar membrane. Effectors are transported via a pathogen-derived translocon into the erythrocyte. (D) The nematode stylet mechanically pierces the host cell wall but does not pierce the host membrane. Secretions from the esophageal glands are released into the stylet and may be deposited outside the host plasma membrane or injected into the cytoplasm of the host cell through the stylet orifice. The mechanism of effector delivery into the host via these structures is described with relevant GO terms, labeled with the same letters as those in the structure.

host via substance secreted by type IV secretion system" (210).

Eukaryotic Effector Delivery Systems

Parallels to bacterial type II and type III secretion occur among eukaryotic symbionts. For example, as in the type II secretion of bacterial toxins, plant-pathogenic fungi and oomycetes secrete effectors that have the intrinsic ability to cross host plasma membranes into host cells. Analogous to type III secretion, plant-pathogenic nematodes insert a needle-like stylet into host plant cells that, depending on the species, delivers effectors into the apoplast or symplast and extracts nutrients.

Most fungal and oomycete effectors are secreted through the endoplasmic reticulum (ER)/Golgi complex and, by means of exocytosis, are released into the extracellular milieu. For intercellular plant pathogens such as the fungus *Cladosporium fulvum*, the extracellular milieu is the apoplastic space (198). For pathogens that invade host cells via haustoria (specialized feeding structures) (Fig. 5B) (e.g., powdery mildew and rust fungi and the oomycetes *Hyaloperonospora arabidopsidis*, *Phytophthora infestans*, and *Phytophthora sojae*) and via invasive hyphae (e.g., the fungi *Magnaporthe oryzae* and *Colletotrichum higginsianum*), the extracellular milieu is the extrahaustorial matrix or the extrainvasive hyphal space, respectively (133, 163). A second step involves the translocation of these effectors from the extracellular milieu into the plant cell. The ability of effectors from eukaryotic phytopathogens to act intracellularly has historically been inferred indirectly from the fact that they trigger defense responses mediated by host-encoded cytoplasmic resistance (R) proteins. Most eukaryotic effectors are secreted via the well-characterized ER/Golgi pathway, based on the presence of a predicted secretory signal at the N termini of the proteins. However, some effectors appear to be secreted without utilizing a secretory signal (174). The mechanism of the second step, effector uptake by the eukaryotic host, is under active study. Current research has revealed the presence of host cell-targeting signals (HTSs) in effectors from oomycete and fungal pathogens and the malaria parasite *P. falciparum* (51, 73, 96, 100, 226). A pathogen-derived translocon has been shown to transport the HTS effectors from *Plasmodium* into the erythrocyte (45). In contrast, a recent study showed that for oomycetes and fungi, effectors with the RXLR HTS utilize RXLR-mediated binding to cell surface phosphatidylinositol-3-phosphate (PI3P), followed by lipid raft-mediated endocytosis to enter plant and animal cells (100).

The stylet, a feeding structure found in plant-pathogenic nematodes, including the sedentary cyst (*Heterodera* and *Globodera*) and root knot (*Meloidogyne*) nematodes, can be considered another form of eukaryotic effector translocon. In addition to their role in nutrient uptake, the stylets of cyst nematodes and root knot nematodes have been shown to be involved in direct effector delivery into the plant host (41, 93). While there is no doubt that cyst nematode proteins are introduced across the host plasma membrane, this remains to be formally demonstrated for the root knot nematodes, although it is clear that proteins secreted from the root knot nematode stylet do accumulate in the apoplast.

Finally, apicomplexan parasites deliver effectors directly into the host cell cytoplasm via rhoptries or Maurer's cleft (MC). An overview of eukaryotic secretory systems will be given below, with a focus on the pathosystems described above and how the GO best describes the commonalities among these systems.

Haustoria and parasitophorous vacuoles. Many plant-associated obligate biotrophs (that require growth on living tissues) and some hemibiotrophs (that initially live as biotrophs and later transition to living on dead tissue) form a specialized structure called the haustorium, which establishes intimate contact with a host cell (Fig. 5B). Haustorium-forming symbionts include fungi (e.g., powdery mildew and rust fungi) and oomycetes (e.g., downy mildew pathogens and *Phytophthora* species). During infection, a pathogen hypha penetrates the cell wall and invaginates the plasma membrane of a host cell, whereupon the hypha differentiates into a haustorium. The haustorium is surrounded by the haustorial wall (a modified symbiont cell wall), a region known as the extrahaustorial matrix, and the extrahaustorial membrane, which originates from the host plasma membrane (27, 49). The intracellular obligate parasite of humans *P. falciparum* causes malaria and forms a specialized structure when entering a host cell during the blood stage of infection. This structure, the parasitophorous vacuole (PV) (Fig. 5C), is functionally analogous to the haustorium of biotrophic fungi and oomycetes. As in the formation of haustoria by plant symbionts, the malaria parasite does not pierce the membrane of the erythrocyte but remains enveloped within the host-derived parasitophorous vacuolar membrane (PVM) (146). GO Cellular Component terms available to describe the structure of the PV include "GO:0020003 symbiont-containing vacuole," "GO:0020004 symbiont-containing vacuolar space," and "GO:0020005 symbiont-containing vacuole membrane." Similar terms such as "GO:0085035 haustorium" and "GO:0085036 extrahaustorial matrix" are available to describe different gene products that are components of the haustorium. The haustorium has an additional role in nutrient acquisition (71), and symbiont proteins involved in that role can also be described by using GO terms like "GO:0052094 formation by symbiont of haustorium for nutrient acquisition from host" (30). This function is achieved in the case of *Plasmodium* by a membranous network, which extends from the PVM into the erythrocyte and is called the tubovesicular network (TVN) (118) (described by the GO term "GO:0085019 formation of symbiont-induced tubovesicular network for nutrient acquisition from host"). For effector proteins to reach the internal membranes or cytosol of the host cell (plant or human), they must cross the pathogen plasma membrane and the enveloping host-derived membrane. The entry of such effectors into the host cell has been corroborated for plant associations by the fact that several haustorially expressed secreted proteins (HESPs; effectors) interact with cytoplasmic nucleotide-binding site and leucine-rich repeat (NBS-LRR) resistance proteins in the host and has been corroborated directly by immunolocalization studies (46, 48, 49). As a first step, effectors with ER-type signal sequences are recruited to the symbiont secretory pathway, and from there they are released to the plasma membrane or extracellular space ("GO:0020005 symbiont-containing vacuolar membrane" and "GO:0085036 extrahaustorial matrix," respectively). The secreted proteins (effectors) traveling this path into the host extracellular milieu can be annotated with terms such as "GO:0085006 interaction with host mediated by symbiont-secreted substance released from symbiont-containing vacuole" and "GO:0085004 interaction with host via secreted substance released from haustorium." These two terms, together with the bacterial terms "GO:0052051 interaction with host via protein secreted by type II secretion system," "GO:0052049 interaction with host via protein secreted by type III secretion system," and "GO:0052050 interaction with host via substance secreted by type IV secretion system," can be collected under the more general term "GO:0052048 interaction with host via secreted substance during symbiotic interaction." Since these eukaryotic effectors must be secreted, the bioinformatic identification of signal peptides required for secretion through the ER has proven a valuable first step to screen for putative effectors encoded in the genomes of most

eukaryotic symbionts (16, 97, 143, 206). This approach led, for example, to the generation of catalogues of secreted proteins (the secretome) from several eukaryotic pathogens, including the malaria parasite *P. falciparum*, the flax rust fungus, and the oomycete pathogens *Phytophthora ramorum*, *P. infestans*, and *P. sojae* (27, 53, 70, 86, 97, 101, 214).

Host-targeting signals. After effector secretion from the pathogen, cytoplasmic effectors must translocate across the encompassing extrahaustorial membrane (haustorium-forming pathogens) or parasitophorous vacuolar membrane (intracellular parasites). Transport across the parasitophorous vacuolar membrane by *P. falciparum* effectors into the host cytosol requires an 11-amino-acid host cell-targeting (HTS) motif ($Rx_1SRxLxE/D/Qx_2x_3x_4$) with a 5-amino-acid PEXEL core (RxLxE/D/Q) that is conserved among diverse proteins. The role of the PEXEL signal sequence in targeting effectors to the host cell was confirmed by the visualization of *P. falciparum*-expressed fluorescently tagged proteins within the cytoplasm of infected erythrocytes in a motif-dependent manner (86, 128). A motif superficially similar to PEXEL, namely, RxLR, was bioinformatically identified in oomycete effectors (18, 19, 96, 173, 214). Bhattacharjee and coworkers (17) showed that the RXLR motif was sufficiently similar to PEXEL that it could function as an HTS in *P. falciparum*. Subsequently, the role of the RXLR motif as a host cell-targeting signal has been confirmed for *Phytophthora*-plant systems (51, 226). The HTS, together with the signal peptide, has enabled genome-wide prediction of the effector secretomes of oomycetes and apicomplexans (96, 216, 226). The RXLR HTS in oomycete effectors has recently been shown to mediate entry into the plant host by binding to the outer surface membrane phospholipid PI3P (100). Subsequent entry into the host cells occurs via lipid raft-mediated endocytosis and does not require any pathogen-derived machinery (51, 100), analogous to the entry of several T2SS-secreted bacterial toxins into animal cells via endocytosis following binding to glycolipids (140, 184). Several fungal effectors also use the same mechanism to enter plant cells (100, 172). The GO terms "GO:0085006 interaction with host mediated by symbiont-secreted substance released from symbiont-containing vacuole" and "GO:0085004 interaction with host via secreted substance released from haustorium" can be used to describe effectors that travel across these symbiont-induced structures to the host and to compare them to those traveling via the well-defined bacterial secretion systems.

The nematode stylet. In plant-parasitic nematodes, secretions are synthesized in the esophageal subventral and dorsal glands and released directly into the host cell via a hollow spear-like structure, the stylet. The direct injection of secretions via the stylet, which includes effectors (also called parasitism proteins), is analogous to the injection of bacterial effectors via the T3SS injectisome (29, 208). The stylet also serves as a feeding structure, withdrawing nutrients from the host cytoplasm (195). The stylet in the cyst nematode mechanically pierces the host cell wall but not the membrane, which becomes invaginated around the stylet tip to provide an opening exclusively at the stylet orifice (Fig. 5D) (196). Secretions from the stylet can transform root cells in susceptible plants into metabolically active feeding cells, a process that can be described with "GO:0044005 induction by symbiont in host of tumor, nodule, or growth" (208, 222). Analogous to terms used to describe other mechanisms of effector delivery discussed above, "GO:0085003 interaction with host via secreted substance released from stylet" is an appropriate term to describe the mechanism of effector delivery into host cells via the stylet (29, 208).

Alternative mechanisms of eukaryotic effector transport. Alternative mechanisms of transport by fungal, oomycete, and apicomplexan pathogens have been noted. The rhoptries, one of the apical secretory organelles in apicomplexans, secrete rhoptry proteins (ROPs), which include effectors, into the host in the early minutes of parasite invasion (22, 26, 72). The ROPs in *Toxoplasma gondii* include factors that may be vital for the formation of the parasitophorous vacuole as well as protein kinases and phosphatases (183). One of the phosphatases, protein phosphatase 2C (PP2C-hn), contains a nuclear localization signal, which indicates that PP2C-hn is imported into the nucleus after delivery into the host cytosol by the rhoptry organelle (64). Some proteins also associate with *P. falciparum*-induced membranous structures (MCs) found in the cytoplasm of the erythrocyte (117). MCs extend from the PVM to become distributed beneath the erythrocyte plasma membrane and, in some cases, transport proteins to the erythrocyte surface (227). Proteins resident in MCs include PEXEL-containing (KAHRP and PfEMP3) and PEXEL-independent (SBP1, MAHRP1, and REX1) proteins (37, 157, 182, 197, 223). Proteins making up Maurer's clefts and rhoptries can be described with the GO Cellular Component terms "GO:0020036 Maurer's cleft" and "GO:0020008 rhoptry," respectively. Terms to describe effector delivery via Maurer's clefts and rhoptries are "GO:0085009 interaction with host mediated by symbiont-secreted substance released from Maurer's cleft" and "GO:0085007 interaction with host via secreted substance released from rhoptry," respectively.

The fungal powdery mildew effectors Avr-a10 and Avr-k1, which are recognized by the cytoplasmic host resistance proteins MLA10 and MLK (174), lack the N-terminal signal peptide and must presumably be secreted via an alternative secretory pathway. In addition, non-haustorium-producing fungi such as the rice blast fungus *M. oryzae* produce biotrophy-associated secreted (BAS) proteins, which cross the extrainvasive hyphal membrane and accumulate together with known effectors in the extrainvasive hyphal space (102, 141). The terms "GO:0085039 extrainvasive hyphal membrane," " GO: 0085040 extrainvasive hyphal space," and "GO:0085005 interaction with host via secreted substance released from invasive hypha" are a few of the terms needed to describe the common theme shared with the haustorium-forming counterparts.

Microbial symbionts use a diversity of machinery to secrete proteins that interact with the biotic environment of their host. However, as we have shown in this section, there are structural similarities as well as common functional roles among these secretion systems that can be captured by GO annotation. Ultimately, effectors from the diverse symbiont-host interactions discussed above are distinguished by specific GO terms related to the structures involved in delivery into the host. These specific GO terms are collected under the umbrella of a parent term, "GO:0052048 interaction with host via secreted substance during symbiotic interaction." Gene annotations from diverse symbionts associated with GO:0052048 are visible

in the GO browser AmiGO. In addition, gene products associated with symbiont-induced structures such as Maurer's cleft and the parasitophorous vacuole are also described with specific Cellular Component ontology terms, "GO:0020036 Maurer's cleft" and "GO:0020003 symbiont-containing vacuole." Curators use these terms to describe specifically the site of action of symbiont gene products when supported by experimental evidence. In a search for "GO:0020036 Maurer's cleft" and "GO:0020003 symbiont-containing vacuole" with the AmiGO browser, users can trace these specific terms up the DAG to a more general term, "GO:0033655 host cell cytoplasm part," which includes other structures found in the host cytoplasm that may serve as action sites for symbiont gene products. Effectors delivered into the host can either trigger or suppress the host defense mechanisms. The process of immunity activation or suppression is the subject of discussion in the sections below.

IMMUNITY IN PLANTS AND ANIMALS

Immune systems comprise layered sets of defenses that protect plants and animals against infection (5, 39, 98, 113, 114, 148, 158, 237). Physical structures act at the forefront, creating barriers to prevent ingress into the host. These structures include the cuticle and cell wall in the case of plants (reviewed in references 85, 90, and 209) and skin and mucosal membranes in the case of animals (132). Physical barriers to host entry are described by GO terms, most notably those found in the Cellular Component ontology. For example, the term "GO:0005618 cell wall" can be used to describe gene products associated with the cell wall in the plant host, and "GO:0016020 membrane" is a more general term that encompasses protective barriers such as the mucosal membrane in the human host. Gene products acting intrinsically in different parts of the cell in plants or animals are subsumed under the parent term "GO:0044464 cell part." On the other hand, if a microbe gene product is associated with the host cell wall or membrane, the microbial gene product is annotated with the terms "GO:0044158 host cell wall" and "GO:0033644 host cell membrane," which form part of a larger set of terms that lie under "GO:0043657 host cell."

Where these physical barriers are breached, innate immunity, which is the first line of inducible defense against infection, provides an immediate but relatively nonspecific response. One branch of innate immunity in plants shares several similarities with mammalian innate immunity. One similarity is that both are activated by microbial molecules referred to as microbe-associated molecular patterns (MAMPs) (also referred to as pathogen-associated molecular patterns [PAMPs] in the case of pathogens). MAMPs are perceived in both plant and animal hosts by pattern recognition receptors (PRRs) on the host cell surface (32, 98). Examples of MAMP-PRR interactions in plants include the well-characterized one between the peptide flg22 from bacterial flagellin (the main protein component of flagella) and its *Arabidopsis* receptor FLS2 (flagellin sensitive 2), the one between elongation factor Tu (EF-Tu) and the elongation factor receptor (EFR) (237, 238), and the one between fungal chitin and chitin elicitor receptor kinase 1 (CERK1) (136, 220, 221). Other MAMPs include cell wall β-glucans, transglutaminase, and secreted elicitin lipid transfer proteins found in some oomycetes (23, 84, 150, 169). Analogous to MAMP recognition in plants, diverse MAMPs from bacteria, fungi, and viruses are recognized in animals by Toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) (which are intracellular) (reviewed in reference 114). MAMPs such as bacterial flagellin can be recognized by both plants (FLS2 receptor) and animals (TLR5 receptor) albeit via different epitopes (13).

The GO annotation of proteinaceous MAMPs utilizes terms in the Biological Process ontology such as "GO:0051701 interaction with host" (Fig. 6) and, in most instances, the slightly more specific term "GO:0044044 interaction with host via substance in symbiont surface." In cases where the substance is secreted or released from a specialized structure in the symbiont, the terms "GO:0085002 interaction with host mediated by secreted substance released by symbiont from symbiotic structure" and its child terms would be appropriate to describe them. In general, these recognition-related terms for MAMPs are not very detailed because their recognition by the host is not a specific function of the microbe. MAMPs normally have other specific functions that would be described by the appropriate terms. For example, flagellin would be described with "GO:0060286 flagellar cell motility." The recognition of MAMPs by hosts is, however, a specific function, and there are many terms available for the description of host defense and immune responses. For example, the host PRRs interacting with MAMPs can be annotated by using terms found under the parent term "GO:0051702 interaction with symbiont." The GO terms "GO:0051855 recognition of symbiont" and "GO:0006952 defense response" appropriately describe the various PRRs involved in the detection of microbes via MAMPs. Additionally, flagellin PRRs could be annotated with "GO:0042742 defense response to bacterium." In each case, the identity of the interacting organism, where appropriate, can be described through the inclusion of its taxon ID in the taxon field of the annotation report. As in a number of areas, additional GO terms to describe the functions of MAMPs and PRRs are still needed. Members of the community are encouraged to contribute to this goal.

Accumulating evidence indicates that MAMP recognition by Toll and interleukin-1 (IL-1) receptors (TIRs) in animal hosts leads to the recruitment of several TIR domain-containing adaptors, such as MyD88, TIRAP, TRIF, and TRAM (reviewed in references 10 and 225). In plant systems, a receptor kinase-like adaptor protein, BAK1 (BRI1-associated receptor kinase 1), that links FLS2 and EFR activation to intracellular signal transduction has been identified (31). These associated receptor-like adaptor kinases can be annotated with "GO:0002758 innate immune response-activating signal transduction" and "GO:0075110 positive regulation by symbiont of host receptor-mediated signal transduction" from the GO Biological Process ontology. These complexes eventually trigger downstream signaling, resulting in the activation of immune responses (5, 58, 147). Mitogen-activated protein (MAP) kinase (MAPK) cascades have emerged as a universal signal transduction mechanism that connects diverse PRR-coreceptor/adaptor complexes to cellular and nuclear responses to infection in both plants and animals. Using a leaf cell assay

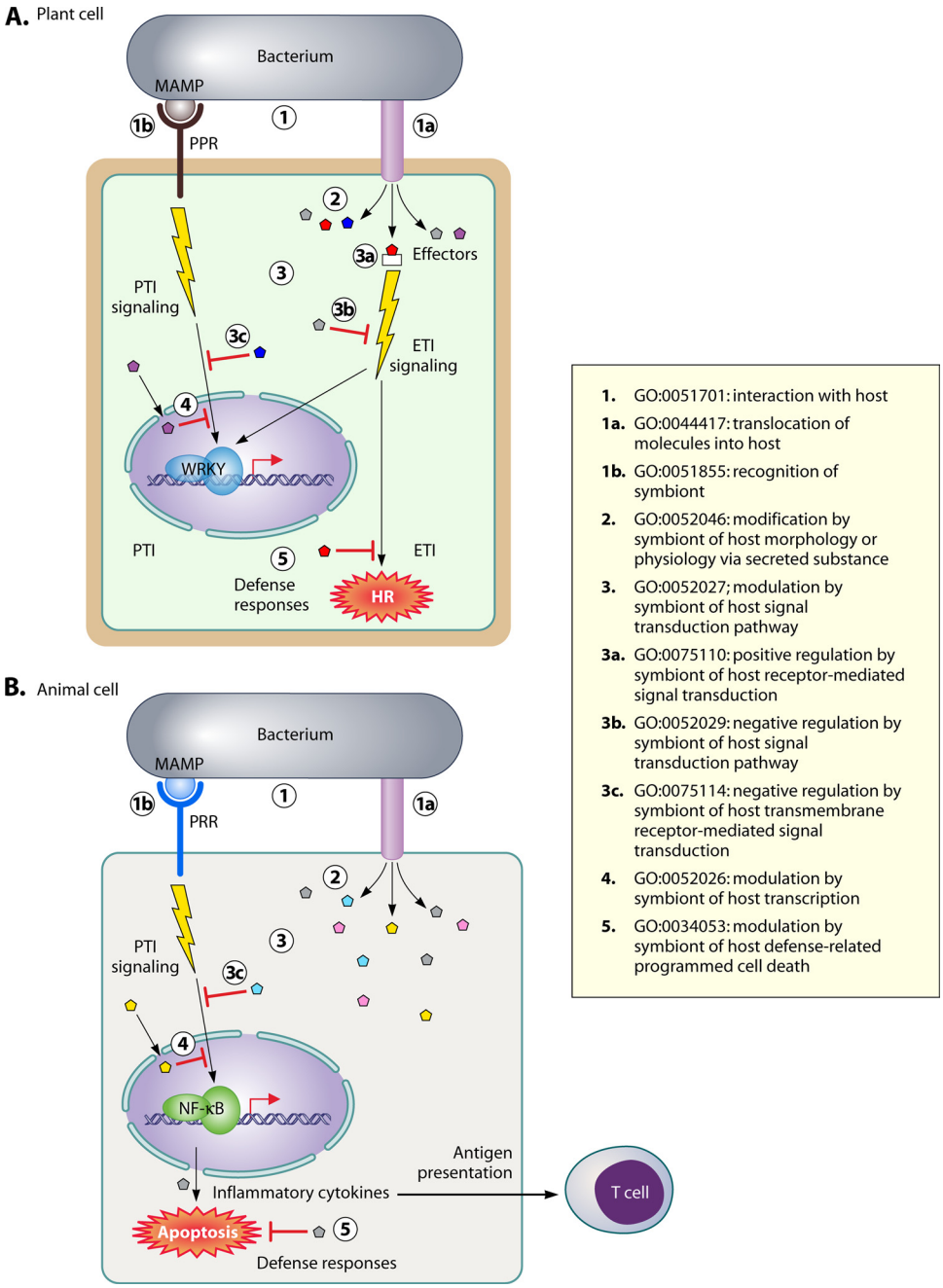

FIG. 6. Simplified representation of innate immunity in plant and animal hosts showing some relevant GO terms. MAMP, microbial (or pathogen)-associated molecular patterns; PRR, pattern recognition receptor; PTI, PAMP (MAMP)-triggered immunity; ETI, effector-triggered immunity; WRKY, a class of plant transcription factors; NF-κB, an animal transcription factor; HR, hypersensitive response. Additional relevant GO terms may be found as children of "GO:0044003 modification by symbiont of host morphology or physiology."

based on the flg22-inducible transcription of early response genes in *Arabidopsis* mesophyll protoplasts, Asai and coworkers (11) identified a complete MAPK signaling cascade and WRKY transcription factors that function downstream of the flagellin receptor. Similarly, in the innate immune system of humans, MAMP perception triggers the cascade of signaling pathways and activates MAP kinases such as p38, Jun N-terminal protein kinases (JNKs), and extracellular signal-regulated kinase 1 (ERK1), ultimately leading to the activation of several transcription factors, which in turn induce the transcription of inflammatory cytokines, type I interferons, and chemokines (5, 115). The components of these signal transduction pathways can also be described with "GO:0002758 innate immune response-activating signal transduction" and "GO:0075110 positive regulation by symbiont of host receptor-mediated signal transduction" as well as "GO:0000165 MAPKKK cascade."

Well-adapted microbial pathogens have found ways to avoid,

tolerate, or suppress the first line of defense (innate immunity) in plants and animals, thus necessitating the establishment of additional lines of defense. The additional lines of defense are termed acquired or adaptive immunity in the case of higher vertebrates and effector-triggered immunity (ETI) in the case of plants. ETI, also known as resistance (*R*) gene-mediated resistance, is nonadaptive and so is considered a second level of innate immunity. Vertebrate adaptive immunity and ETI have been characterized as triggering a more amplified and accelerated form of defense. ETI is initiated through the recognition of microbial virulence factors (effectors) and is commonly mediated via intracellular receptors carrying nucleotide-binding sites and leucine-rich repeats (NBS-LRR proteins) (47). These NBS-LRR proteins are encoded by *R* genes and are often polymorphic in plant populations. Some *R* genes do not encode NBS-LRR proteins but instead encode PRR-like molecules or proteins activated by microbial effectors with transcription factor activity (104, 119, 205). ETI is typically a much stronger response than PAMP-triggered immunity (PTI) and often includes a hypersensitive response (HR) that involves localized programmed cell death. In animals, innate and adaptive immunities are linked because MAMP responses include the stimulation of antigen presentation to T cells, which is required to trigger adaptive immunity (6, 87, 233). T lymphocytes carrying receptors of the appropriate specificity proliferate and mature in response to the presented antigen and either kill the pathogen directly or secrete cytokine mediators that stimulate further immune responses, including the activation, proliferation, and maturation of B lymphocytes. B lymphocytes provide humoral immunity by releasing antibodies specific for the pathogen. Eventually, a small number of antigen-specific "memory" B cells remain, which establish long-term immunity in case the host is reexposed to the pathogen (reviewed in reference 113). In plants, a nonspecific and short-term memory is provided by MAMP-induced systemic acquired resistance or immunity (SAR) (135). SAR allows plants to "remember" a primary infection and deploy enhanced defenses to a secondary infection at sites remotely located from the initial infection, giving rise to elevated systemic resistance to subsequent pathogen encounters (reviewed in reference 218). SAR is nonspecific, so an encounter with one pathogen can trigger elevated resistance to unrelated pathogens.

A large number of GO terms have been developed by the PAMGO consortium to describe microbial gene products that trigger signaling pathways and other responses associated with immunity (Fig. 6). These can be found under the node "GO:0044003 modification by symbiont of host morphology or physiology." Microbial gene products that trigger specific components of the signaling pathways and defense responses in the host are described with terms beginning with "positive regulation" (synonyms include activation and upregulation). Terms describing the activation of different components of the signaling pathways and immune response include "GO:0052389 positive regulation by symbiont of defense-related host calcium ion flux," "GO:0052079 positive regulation by symbiont of defense-related host MAP kinase-mediated signal transduction pathway," and many others, which describe the responses that symbionts trigger in animal or plant hosts. "GO:0034053 modulation by symbiont of host defense-related programmed cell death" has two child terms that describe the symbiont modulation of different types of programmed cell death (PCD) in plant and animal hosts. These terms are "GO:0085048 positive regulation by symbiont of host plant-type hypersensitive response" and "GO:0052151 positive regulation by symbiont of host apoptosis," respectively. Furthermore, the more general term "GO:0052553 modulation by symbiont of host immune response" encompasses more-granular terms like "GO:0052163 modulation by symbiont of defense-related host nitric oxide production" and "GO:0052164 modulation by symbiont of defense-related host reactive oxygen species production," both of which are associated with defense responses in both plants and animals. Terms like "GO:0052154 modulation by symbiont of host B-cell-mediated immune response" and "GO:0052165 modulation by symbiont of host phytoalexin production" are specific for animal and plant immunity, respectively. As part of the development of GO terms for plant-associated microbes, terms have been created to describe the processes of MAMP- and effector-triggered immunity. However, the comprehensive inclusion of terms for describing adaptive immune processes within the "GO:0051701 interaction with host" node awaits more focused attention from immunologists.

EFFECTORS AT WORK

Recent research has brought to light the critical role played by effector proteins (referred to as virulence factors in the animal pathology field) from diverse symbionts in creating a proliferation-permissive environment within animal and plant hosts. These effectors commonly target host defense signaling pathways in order to suppress defense responses. Others target the gene expression machinery or trigger specific modifications of host morphology or physiology that promote the nutrition and proliferation of the symbiont. GO terms describing various forms of modification of host processes by symbionts are collected under the term "GO:0044003 modification by symbiont of host morphology or physiology." The specific processes that contribute to the immunity of plants and animals to diverse symbionts are still being unraveled. However, ongoing characterization of individual effectors and their targets in host cells has provided new insights into host defense mechanisms. In the sections below, more detailed GO terms are discussed that illustrate several commonalities in effector functions in plant and animal symbionts (Fig. 6).

Targeting of the Host Surveillance Receptors

MAMP receptors and receptor-adaptor complexes are a major target for symbiont effectors. Among bacterial plant pathogens, type III effector proteins have been implicated in the disruption of receptor-mediated MAMP recognition. For example, the bacterial *Pseudomonas syringae* pv. *tomato* effector AvrPto interacts directly with the *Arabidopsis* MAMP receptors FLS2 and EFR (228), thereby inhibiting the kinase activity of the receptors (229). Additionally, both AvrPto and another *P. syringae* effector, AvrPtoB, physically interact with the kinase domain of the coreceptor BAK1, blocking MAMP receptor signaling and thus inhibiting plant immunity (192). Interference with receptor interactions is also observed for animal

pathogens. *Brucella* spp., causal agents of brucellosis in animals, interfere with defense signaling through the deployment of a TIR domain-containing protein (TcpB). TcpB is believed to interfere with the primary function of the Toll-like receptor (TLR) adaptor TIRAP by mimicking its properties to subvert TLR signaling (170). Related receptor-ligand interactions play an analogous role in mediating mutualistic interactions. For example, during the interaction between leguminous plants and nitrogen-fixing rhizobial bacteria, PRR-like receptors in the plant recognize a soluble lipooligosaccharide (Nod factor) produced by the bacteria that triggers nodule development in plant roots (125, 171, 236).

Effectors that interfere with MAMP-induced defense signaling can be collectively annotated with the term "GO:0052034 negative regulation by symbiont of microbe-associated molecular pattern-induced host innate immunity," while interactions with specific MAMP receptors, adaptors, or receptor-adaptor complexes can be described by using "GO:0075345 modification by symbiont of host protein." The specific biochemical action on the host protein, where characterized, can be described with child terms such as "GO:0044031 modification by symbiont of host protein by phosphorylation" and "GO:0075346 modification by symbiont of host protein by ubiquitination."

Manipulation of Signaling Complexes or Pathways in the Host

In both plant and animal systems, complex signaling pathways mediate the response to detected symbionts, with elements of the signaling pathways representing the most common targets for effector-mediated suppression of the immune response. In the GO database, effectors that target signal transduction in the host are generally annotated with the term "GO:0052027 modulation by symbiont of host signal transduction pathway" (208). In some cases, the effector and target have been more extensively characterized, supporting annotation with more-specific child terms. In other cases, the effectors in question await in-depth evaluation. Activation of mitogen-activated protein kinases (MAPKs) is one of the earliest signaling events following MAMP recognition in both plants and animals, making MAPK activation an effective target for effectors. In mammalian pathosystems, effectors targeting MAPK signaling include the YopJ and YopP proteins of pathogenic *Yersinia* species (77, 144, 154, 155) and AvrA and SpvC of *Salmonella* (36, 99, 130). The effector HopAI1 from the bacterial plant pathogen *P. syringae* pv. *tomato* is a phosphothreonine lyase that dephosphorylates the MAPKs MPK3 and MPK6 to inhibit MAMP receptor signaling in *Arabidopsis* plants (235; reviewed in reference 39). Several *Salmonella* effectors suppress cellular immune responses by reversing phosphorylation by host MAPKs (121, 145). Given that the *P. syringae* effector HopAI1 also interferes with host MAP kinase phosphorylation, this is a nice example of a common mechanism of modulation of host immune responses shared by symbionts of plants and mammals. Effectors disrupting MAPK signaling associated with either animal or plant immunity can be annotated with the term "GO:0052078 negative regulation by symbiont of defense-related host MAP kinase-mediated signal transduction pathway." Other signaling pathways targeted by effectors include the nuclear factor κB (NF-κB) signaling pathway, which plays a role in animal host immunity, and hormone-mediated defense signaling pathways in plants. For example, the *Yersinia* effector YopJ (77, 144, 154, 155) and the *Salmonella* effector AvrA (99), in addition to interfering directly with MAPK signaling pathways, also inhibit NF-κB-mediated signaling. This role can be described with "GO:0085034 negative regulation by symbiont of NF-κB-mediated signal transduction pathway." In plants, the hormones ethylene, jasmonic acid, and salicylic acid play central roles in defense signaling, with the activation of salicylic acid-dependent pathways and programmed cell death (PCD) representing the primary defense mechanisms against biotrophic pathogens and with jasmonic acid and ethylene signaling pathways mediating defense against necrotrophs (pathogens gaining their nutrition from dead tissues) (65). Several *P. syringae* effectors have been shown to interfere with salicylic acid and ethylene signaling (35, 44).

While GO terms describing processes at various levels of specificity are available to annotate effectors that target specific signaling pathways found only in animals (e.g., NF-κB mediated), only in plants (e.g., ethylene mediated), or in both hosts (e.g., MAPK mediated), all of these terms are child terms that share a parent term, "GO:0052027 modulation by symbiont of host signal transduction pathway." Therefore, this parent term together with its various child terms can be used to identify and collect effectors of plant and animal symbionts that share this common mechanism.

Interference with the Host Cytoskeleton

The cytoskeleton is a complex and highly dynamic three-dimensional scaffold found in all eukaryotic cells and is comprised of filamentous polymers (actin filaments and microtubules) (129, 164). In addition to its general structural role, the cytoskeleton acts in strengthening plant and animal cellular barriers against symbionts (25, 187, 188). Rapid changes occur in the architecture of the cytoskeleton during host-microbe interactions. While these rearrangements may in some cases advance mutualistic associations (231), they are also required for the execution of defense responses against pathogens. Effectors secreted from mammalian pathogenic bacteria via the T3SS target the host cytoskeleton directly by interactions with tubulin or actin or indirectly by manipulating regulatory proteins such as small Rho GTPases. A few specific examples follow. The human enteropathogenic Gram-negative bacterium *Salmonella* delivers a subset of SPI-1 effectors that act in concert to induce host membrane deformation and a rearrangement of the underlying actin to facilitate the entry of the bacteria into parasitophorous vacuoles (*Salmonella*-containing vacuoles [SCVs]) (83, 159, 160, 167). *Shigella* depletes microtubules at the site of bacterial invasion by releasing an effector, VirA, that interacts with tubulin heterodimers (232). Studies employing mutants of several *Yersinia* outer proteins (Yops) revealed that YopE, YopH, and YopT act in concert to rapidly damage the actin cytoskeleton of dendritic cells, potentially inhibiting the phagocytic function of these cells (4). Interestingly, phytopathogenic effector proteins that interfere with the host cytoskeleton have not yet been identified. However, immunofluorescence and microscopy techniques have enabled

the visualization of host cytoskeleton alterations in response to several pathogens (80, 201, 202). For example, a reorganization of the cytoskeleton occurred when the *Arabidopsis* penetration 1-1 (*pen1-1*) mutant was inoculated with a virulent species of powdery mildew (202). A recent study identified AtADF4, a member of the actin-depolymerizing factor (ADF) family of proteins that in part regulates the dynamic behavior of actin filaments, as a novel signaling component in the AvrPphB-RPS5-mediated defense signal transduction pathway in the interaction between *Pseudomonas syringae* pv. *phaseolicola* and *Arabidopsis*. The loss of AtADF4 leads to an enhanced susceptibility of *Arabidopsis* to *P. syringae* pv. *phaseolicola* expressing AvrPphB (204), indicating the involvement of the actin cytoskeleton in plant resistance to this pathogen. Currently, no effector abrogating AtADF4 function has been identified. The GO term appropriate for describing gene products involved in the modification of the host cytoskeleton is "GO:0052039 modification by symbiont of host cytoskeleton," which is a child term of "GO:0052043 modification by symbiont of host cellular component."

Manipulation of Programmed Cell Death

The GO defines PCD as "cell death resulting from activation of endogenous cellular processes." This term is intended for describing the role of PCD in normal cell growth, development, and homeostasis intrinsic to an organism (28). In addition to these endogenous roles, plants and animals use PCD as a weapon against biotrophic pathogens that require living host tissue. Defense-related PCD involves a series of biochemical events leading to characteristic cell morphologies and death. Different types of defense-related PCD have been defined for both plants and animals. These include the hypersensitive response in plants and apoptosis, pyroptosis, and autophagic cell death in animals. The different kinds of PCD in animals depend on the nature of the symbiont and the site of colonization (reviewed in reference 116). In the GO database, terms describing different types of endogenous PCD are collected under the parent term "GO:0012501 programmed cell death." These terms include "GO:0006915 apoptosis" and "GO:0048102 autophagic cell death." To differentiate PCD induced by symbionts from endogenous PCD, the term "GO:0034050 host programmed cell death induced by symbiont" was added as a child of "GO:0012501 programmed cell death."

To counteract defense-related PCD, many biotrophic or intracellular pathogens have evolved effective mechanisms to block PCD. For example, the obligate intracellular human bacterium *Rickettsia rickettsii* requires viable host cells to thrive and replicate. *R. rickettsii* cells stimulate NF-κB signaling in host cells, and this activation turns on a program of gene expression that keeps cells proliferating and inhibits apoptosis triggered by conditions that would otherwise cause the cells to die (34). Conversely, symbionts that thrive on dead cells may promote PCD for their benefit. For example, bacteria such as *Bacillus anthracis* and *Pseudomonas aeruginosa* produce cytotoxic pore-forming exotoxins that promote cell death by killing macrophages before the bacterial cells are phagocytosed and destroyed (76, 140). Interesting parallels can be drawn for plant pathosystems. For example, many effectors from the bacterium *Pseudomonas syringae* pv. *tomato*, including HopAB2 (AvrPtoB) (3, 69), and also several effectors from the oomycete *Phytophthora sojae*, including Avr1b (50), can inhibit defense-like PCD triggered in plants by other effectors or by the proapoptotic mammalian BAX protein. Similarly, the effector Avr3a from the oomycete *Phytophthora infestans* can suppress PCD triggered by the MAMP INF1 in *Nicotiana benthamiana* (21). Each of these three pathogens is hemibiotrophic. To establish an infection, they require living tissue and hence must suppress PCD. Later in infection, they become necrotrophs and promote PCD. The Nep1-like protein toxin NLP_{Ps} (previously called PsojNIP) is induced in *P. sojae* during the transition from biotrophy to necrotrophy; the toxin promotes cell death in soybean, presumably to benefit the necrotrophic growth of the pathogen. Effectors from plant and animal pathogens that suppress PCD may be described with "GO:0034054 negative regulation by symbiont of host defense-related programmed cell death," while those (including toxins) promoting PCD may be described with "GO:0034055 positive regulation by symbiont of host defense-related programmed cell death" (122, 208).

Hijacking of the Host Ubiquitination Machinery

Ubiquitination regulates many essential cellular processes, including protein degradation by the proteosome and endocytosis from the plasma membrane. Ubiquitination results in the addition of ubiquitin to internal lysine residues of the substrate protein in a multistep enzymatic process (66). The ubiquitination process involves a ubiquitin-activating enzyme (E1), which transfers ubiquitin to a family of ubiquitin-conjugating enzymes (E2s). Ubiquitin-loaded E2s are then recruited to their substrates by a family of ubiquitin ligases (E3s), which play a critical role in substrate recognition. Several pathogens interfere with or exploit the host ubiquitin pathway in order to evade or suppress immune responses (52). *Salmonella enterica*, which causes gastrointestinal disease in humans and animals, secretes several T3Es that exploit the ubiquitin pathway. These include SopA and SspH2, which are E3 ligases and potentially attach ubiquitin to a lysine on a protein target, ultimately resulting in its degradation. Manipulation of the ubiquitination status of host proteins has also been observed among effectors deployed by plant pathogens. Most notably, the *P. syringae* pv. *tomato* effector AvrPtoB protein exhibits E3 Ub ligase activity in its C-terminal domain. This activity of AvrPtoB facilitates the ubiquitination of the host resistance (R) protein kinase Fen, targeting it for degradation and contributing to the suppression of immunity (2, 95). The *P. syringae* effector HopM1 also mediates the destruction of an immunity-associated protein, redirecting the *Arabidopsis* protein AtMIN7 to the host's own ubiquitination/proteasome system by a mechanism that is not yet understood (149). The effector XopD, encoded by the bacterial plant pathogen *Xanthomonas campestris* pv. *vesicatoria*, is an active cysteine protease with plant-specific SUMO (small ubiquitin-like modifier) substrate specificity, thus mimicking an endogenous plant SUMO isopeptidase (88). XopD locates to the nucleus, suggesting that it may modify the plant transcription machinery (107). The term "GO:0075345 modification by symbiont of host protein" can be used to describe all such effectors that modify host proteins, with child terms such

as "GO:0075346 modification by symbiont of host protein by ubiquitination" applied when the nature of the modification has been demonstrated.

Manipulation of Host Transcriptional Machinery

Agrobacterium tumefaciens is a classic example of a symbiont that reprograms its host's transcriptional machinery to facilitate tumor formation. The mechanisms underlying this reprogramming are largely unknown. However, studies show that the T4SS effector VirE3, which localizes to the plant nucleus, has *trans*-activating activity in yeast and binds a general plant-specific transcription factor, pBrp (60). These characteristics led some authors to suggest that VirE3 may function as a transcriptional activator mediating the expression of genes involved in tumor development. Other symbiont effectors have also been shown to function as transcription factors in the nucleus, altering the host transcriptome by mimicking host transcriptional activators. For example, a family of transcription activator-like (TAL) effectors found in some pathogenic bacteria, including *Xanthomonas* spp., appears to activate host genes to enhance host susceptibility. Specific examples include the *Xanthomonas oryzae* pv. *oryzae* TAL effectors PthXo6 and PthXo1, which activate the expression of the rice genes OsTFX1 and Os8N3 to promote virulence in the host (200, 230). An example of a TAL effector that binds directly to a host gene promoter is the *X. campestris* pv. *vesicatoria* effector AvrBs3. In binding to the host promoter, AvrBs3 induces the expression of plant genes, including UPA20, which regulates hypertrophy in susceptible plants (105, 177).

Note that in the GO database, gene products acting directly on host gene transcription as well as those with a more indirect impact could be annotated with the Biological Process term "GO:0052026 modulation by symbiont of host transcription." The biochemical means by which the process is carried out can be distinguished by using annotation with terms from the Molecular Function ontology, e.g., "GO:0003700 transcription factor activity" in the case of AvrBs3.

Most of the examples of effector function discussed above come from bacterial symbionts. More work is needed to experimentally characterize eukaryotic effectors in detail.

APPLICATIONS OF THE GO

Although much of the current discussion has focused on the GO from a curatorial perspective, to many users the true value of the GO can be found in its contribution to the synthesis of original research. This section introduces readers to some of the uses of the GO. The GO Web browser AmiGO (http://amigo.geneontology.org) provides an interface to search and browse the ontology and annotation data provided by the GO consortium. Users can search for terms and view the gene products annotated to these terms. For example, to search for the gene products associated with "GO:0034055 positive regulation by symbiont of host defense-related programmed cell death," if one has prior knowledge of the GO ID, it can be entered into the search box; otherwise, a keyword search using one or more words in the term will be adequate. The results page contains a tab, "gene product associations," that lists records of annotations of genes from diverse organisms made to date. There are filter buttons that enable users to specify particular searches, for example, by "gene product type" or "species." Other tools for searching and browsing the GO database can be found at http://www.geneontology.org/GO.tools.shtml. Various genome databases have incorporated GO annotation data as well. For example, at EuPathDB (Eukaryotic Pathogen Database Resources), a search for the GO term "GO:0044415 evasion or tolerance of host defenses" returns 396 hits, including 1 protein in *Entamoeba invadens*, 1 in *Plasmodium falciparum*, 30 in *Plasmodium vivax*, 270 in *Trypanosoma brucei*, 94 in *Trypanosoma congolense*, and 30 in *Trypanosoma vivax*. Although the current set of annotations may be incomplete, as many organisms have only just undergone genomic characterization, the ability to quickly focus on families of putative proteins that share common features can drive research on topics such as the function of antigenic variation, conserved regions of antigenic proteins, or the evolutionary mechanisms driving such variation within apicomplexan parasites. Indeed, at EuPathDB, once genes of interest have been identified by using the GO, other information is readily accessible, including protein and coding sequences, protein features, orthology data, synteny, BLAST alignments, and so forth. Other microbial databases that feature GO annotations can be accessed through links from the PAMGO website (http://pamgo.vbi.vt.edu/).

Tools that quantify gene expression in the context of GO offer clear benefits to studies of symbiotic interactions because they allow researchers to distinguish among different classes of genes expressed under different experimental conditions. In a recent paper by Kim and coworkers (108), genes expressed during late infection of rice by *Magnaporthe oryzae* were functionally categorized with the GO using InterProScan (234), a tool that allows the querying of sequences against Interpro, a universal protein database (92), and mapping of the output to the GO database. This allows researchers to see the GO-characterized functions of the late-expressed genes and thus generate hypotheses that can subsequently be tested experimentally. In another study, Malmstrom and coworkers (126) used a mass spectrometry-based approach to determine the average number of protein copies per cell for a large fraction of the proteome of the human leptospirosis pathogen *Leptospira interrogans*. The proteins quantified were then grouped into biological functions using the GO. Several tools have been developed to analyze expression data sets with respect to the GO. Since describing these tools is outside the size and scope of the current review, interested readers are encouraged to explore the many tools at the Gene Ontology website (http://www.geneontology.org/GO.tools.microarray.shtml). In addition, to learn more about the applications of the GO, readers are directed to several articles in a special issue of *Trends in Microbiology*, entitled *Gene Ontology for the Microbiologist* (213), which includes, among others, a paper describing knowledge derived from annotating *E. coli* with the GO (89).

CONCLUSIONS

To fully exploit the deluge of genome sequences from host-associated microbes, a universal language that describes the functions of gene products from diverse organisms is essential.

The GO provides such a resource, enabling researchers in different fields to recognize functional similarities among divergent organisms. GO terms developed by the PAMGO consortium have facilitated the description of processes carried out by gene products involved in diverse host-symbiont interactions (http://www.geneontology.org/GO.current.annotations.shtml). While experimental characterization of genes associated with symbioses has recently surged, especially for genes associated with pathogenesis, much more remains to be learned, especially in eukaryotic symbiont interactions. As more knowledge accrues, more evidence-based GO annotations of genes involved in symbiont-host associations can be made. Annotations made with GO terms will facilitate comparative genomics among very divergent symbionts. In particular, by facilitating the identification of analogous processes in diverse microbes, the GO can highlight key functionalities repeatedly required for establishing effective symbioses. These in turn can help focus efforts to prevent or encourage pathogenic or beneficial associations, respectively. GO annotations are also very useful in microarray and proteomic data analyses. The ability to transfer GO annotations from well-characterized gene products to less-characterized ones by analysis of high-throughput data sets presents an opportunity for researchers to generate hypotheses regarding uncharacterized genes. Finally, just as symbionts continue to coevolve with their hosts (plant or animal), GO terms relevant to microbe-host interactions must coevolve with developing knowledge. However, this requires the willingness of the community to add and utilize additional terms describing symbiont-host interactions, especially for animal and human hosts, and we encourage researchers in this area to become involved in this effort. The value of the GO as a uniform language for consistent and informative information exchange is dependent entirely on the willingness of community members to use and to continue to develop it.

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Trudy Torto-Alalibo received her Ph.D. in 2003 from The Ohio State University in Plant Pathology with emphasis in Molecular Biology and Biotechnology and has been working in the area of microbial genomics for the past 10 years. Her dissertation research led to the discovery of a novel superfamily of effectors dubbed the Crinklers from the Irish potato famine pathogen, *Phytophthora infestans.* As a postdoctoral associate at the Virginia Bioinformatics Institute (Virginia Tech) from 2003 to 2004, she worked on the genomics and transcriptomics of *Phytophthora sojae*-soybean interactions and was promoted to the position of a senior research associate and Coordinator of the Plant-Associated Microbe Gene Ontology (PAMGO) project. The PAMGO project has added over 900 terms describing genes involved in microbial-host associations, a valuable resource for the scientific community. Dr. Torto-Alalibo is currently taking time off to spend with her two young boys while working on a few manuscripts.

Candace W. Collmer is a Professor of Biology at Wells College, Aurora, NY, and an Adjunct Professor of Plant Pathology and Plant-Microbe Biology at Cornell University. Her interest in the Gene Ontology (GO) began with a sabbatical project in 2003 to 2004 to annotate genes implicated in virulence in *Pseudomonas syringae* pv. *tomato* DC3000. Training on GO annotation with Michelle Gwinn-Giglio and connecting with investigators from other microbial genome projects led to the group's recognition that new GO terms describing specific processes involved in host-microbe interactions were needed; the PAMGO consortium and the GO term development described here followed. Dr. Collmer earned her Ph.D. in Plant Pathology from Cornell University. She worked as a Research Plant Pathologist in the Plant Virology Laboratory of the USDA/ARS, Beltsville, MD, and as a Research Associate in the Plant Molecular Biology Laboratory of the Boyce Thompson Institute, Ithaca, NY, before joining the faculty of Wells College.

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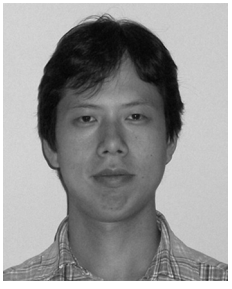
Marcus C. Chibucos majored in Biology and Philosophy at Knox College before receiving his doctorate in Biological Sciences from Bowling Green State University. In the laboratory of Paul F. Morris he characterized polyamine transport kinetics in infective zoospores of the oomycete soybean pathogen *Phytophthora sojae*. As a Postdoctoral Associate in Brett M. Tyler's group at the Virginia Bioinformatics Institute, he worked with the PAMGO consortium to develop Gene Ontology and studied oomycete genomics, contributing to the *Hyaloperonospora arabidopsidis* genome project. Currently, Dr. Chibucos is a Bioinformatics Analyst in the group of Jennifer R. Wortman at the Institute for Genome Sciences in Baltimore, MD. He works on diverse projects, including eukaryotic comparative genomics, the Aspergillus Genome Database, and ontology development, including Gene Ontology, Evidence Code Ontology, and Ontology of Microbial Phenotypes. His involvement with ontologies, which began 5 years ago, arose out of his long-term interest in describing the intricacies of symbiotic interactions.



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Alan Collmer is currently the Andrew J. and Grace B. Nichols Professor in the Department of Plant Pathology and Plant-Microbe Biology at Cornell University. He received his B.A. from Antioch College in 1973 and his Ph.D. from Cornell University in 1981. After doing postdoctoral work in the Department of Biochemistry at Cornell, he joined the faculty of the University of Maryland at College Park for several years before returning to Cornell in 1988. His interests in the type III secretion system and the elusive effector genes of the plant pathogen *Pseudomonas syringae* pv. *tomato* DC3000 led in 2000 to a multi-institutional NSF Plant Genome Research Program sequencing and functional genomics project. Work with project collaborators Robin Buell and Michelle Gwinn-Giglio at The Institute for Genomic Research led to the use of Gene Ontology (GO) terms to annotate virulence-associated genes in DC3000 and participation in the nascent PAMGO project.

Brett M. Tyler is a Professor at the Virginia Bioinformatics Institute and the Department of Plant Pathology, Physiology, and Weed Science, Virginia Tech. He received his Ph.D. in 1981 in molecular biology and immunology from the Walter and Eliza Hall Institute at the University of Melbourne, Australia. After postdoctoral studies in fungal molecular genetics at the University of Georgia, he was a Research Fellow at the Australian National University from 1984 to 1988 and an Associate Professor and Professor at the University of California, Davis, from 1988 to 2002, before joining Virginia Tech. He has worked in the area of plant-microbe interactions since 1987. His group's current research interests are centered on the systems biology of infectious disease, encompassing genome sequencing and transcriptomics of oomycete pathogens, from which the PAMGO project sprung; mechanistic studies of oomycete and fungal effector proteins; new computational tools for analyzing genomic data; and mathematical modeling.